Professional Information

Forminal 500 and 850

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

FORMINAL 500 (TABLETS)

FORMINAL 850 (TABLETS)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FORMINAL 500 - Each film coated tablet contains metformin hydrochloride 500 mg.

FORMINAL 850 - Each film coated tablet contains metformin hydrochloride 850 mg.

Sugar free.

For the full list of excipients refer to section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

FORMINAL 500 is white to off white, round, biconvex film-coated tablets, embossed with 'A' on one side and '115' on other side.

FORMINAL 850 is white to off white, round, biconvex film-coated tablets, with "A" embossed on one side and "117" embossed in one bisect on the other side.

The break line in FORMINAL 850 is only to facilitate breaking for ease of swallowing and not to divide the tablet into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FORMINAL is indicated for:

Type II diabetes mellitus when diet has failed and especially if the patient is overweight.

FORMINAL can be given alone as initial therapy, or can be administered in combination with a sulphonylurea or insulin.

FORMINAL can be used in adults, adolescents and children over 12 of age with Type 2 diabetes mellitus.

4.2 Posology and method of administration

It is important that FORMINAL tablets be taken in divided doses with meals.

Adults:

Initially one 500 mg tablet three times a day, with or after food.

After 10 to 15 days the dose should be adjusted or increased to 850 mg or 1000 mg twice daily.

A slow increase in dose may improve gastro-intestinal tolerability. If control is incomplete a cautious increase in dosage to a maximum of 2550 g daily is justified. Once control has been obtained it may be possible to reduce the dosage of FORMINAL.

Children from 12 years of age and adolescents:

- The usual starting dose is 500 mg or 850 mg once daily with or after food. After 10 to 15 days the dose should be adjusted on the basis of the blood glucose measurements. A slow increase in dose may improve gastro-intestinal tolerability. The maximum recommended is 2000 mg daily, in 2 or 3 divided doses.
- FORMINAL is NOT recommended for use in type 1 diabetes mellitus.

Elderly:

FORMINAL is indicated in the elderly, but not when renal function is impaired. The dose should be adjusted based on renal function.

4.3 Contraindications

- Hypersensitivity to metformin hydrochloride or to any of the excipients
- Diabetic ketoacidosis, diabetic pre-coma, or the history thereof
- Impaired renal function or renal failure (e.g., serum creatinine levels > 135 µmol/L in males and > 110 µmol/L in females or creatinine clearance < 60ml/min)
- Acute conditions with the potential to alter renal function such as:
  - Dehydration,
  - Severe infection,
  - Shock,
  - Intravascular administration of iodinated contrast agents (see 4.4 Special warnings and precautions for use) and
- Chronic liver disease
- History of or states associated with lactic acidosis such as shock or pulmonary insufficiency
- Conditions associated with hypoxia such as cardiac or respiratory failure, recent myocardial infarction, shock, pancreatitis.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism
- Safety in pregnancy and lactation has not been established.
- Children under 12 years old as safety and efficacy have not been established.

4.4 Special warnings and precautions for use

Lactic acidosis:

Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to FORMINAL accumulation. Reported cases of lactic acidosis in patients on FORMINAL have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing also other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

Diagnosis:

Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, metformin should be discontinued, and the patient should be hospitalised immediately.

Renal function:

As FORMINAL is excreted by the kidney, serum creatinine levels should be determined before initiating treatment and regularly thereafter:

- At least annually in patients with normal renal function,
- At least two to four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly subjects.

Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a NSAID.

The administration of FORMINAL may be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet with insulin.

Administration of iodinated contrast agent:

As the intravascular administration of iodinated contrast materials in radiological studies can lead to renal failure, FORMINAL should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Surgery:

FORMINAL should be discontinued 48 hours before elective surgery with general anaesthesia and should not be usually resumed earlier than 48 hours afterwards.

Other precautions:

- All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.
- The usual laboratory tests for diabetes monitoring should be performed regularly.
- Although FORMINAL alone never causes hypoglycaemia, caution is advised when it is used in combination with insulin or sulfonylureas.

4.5 Interaction with other medicines and other forms of interaction

Glucocorticoids (systemic and local routes), beta-2-agonists, and diuretics:

Have intrinsic hyperglycaemic activity. Inform the patient and perform more frequent blood glucose monitoring, especially at the beginning of treatment. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.

ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.

Digitalis glycosides

Hydrochlorothiazide 25 Gulf may enhance the toxicity of digitalis glycosides such as digoxin by depleting serum-potassium concentrations.

Cimetidine:

Reduced renal clearance of FORMINAL has been reported during cimetidine therapy, so a dose reduction should be considered.

Sulphonylurea:

Concomitant therapy of FORMINAL with sulphonylurea may cause hypoglycaemia.

Alcohol:

Increased risk of lactic acidosis in acute alcohol intoxication, particularly in case of:

- fasting or malnutrition,
- hepatic insufficiency.

Avoid consumption of alcohol and alcohol-containing medications.

Iodinated contrast agents:

Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in FORMINAL accumulation and a risk of lactic acidosis.

FORMINAL should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Anticoagulants:

FORMINAL has been reported to diminish the activity of warfarin, and so dose adjustments of FORMINAL should be considered.

Vitamins:

Long-term treatment with FORMINAL may cause vitamin B12 malabsorption in the gastro-intestinal tract, thus a dose reduction of FORMINAL should be considered.

4.6 Fertility, pregnancy and lactation

The use of FORMINAL during pregnancy and lactation is contraindicated as the safety has not been established (see section 4.3).

4.7 Effects on ability to drive and use machines

FORMINAL monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines. Patients should be alerted to the risk of hypoglycaemia when FORMINAL is used in combination with other antidiabetic medicines (e.g. sulfonylureas or insulin).

The ability to drive or to use a machine can be severely affected with the combination of FORMINAL and alcohol consumption.

4.8 Undesirable effects

The following side effects may occur with FORMINAL**.**

Side effects that occur less frequently:

Haematological:

- Megaloblastic anaemia

Genitourinary / Kidney:

- Ketoacidosis and ketonuria

Liver:

- Severe cholestatic hepatitis

Other:

- Hypersensitivity
- Hypoglycaemia

Side effects that occur more frequently:

Haematological:

- Vitamin B12 deficiency

Nervous System disorders:

- Metallic taste

Gastro-intestinal:

- Anorexia, nausea, vomiting, constipation, diarrhoea

Special Precautions:

lactic acidosis associated with the use of FORMINAL. in patients with a metabolic acidosis and not having evidence of ketoacidosis (ketonuria and ketonaemia), lactic acidosis should be suspected and FORMINAL therapy stopped. lactic acidosis is a medical emergency, which must be treated in hospital. FORMINAL is excreted by the kidney and regular monitoring of renal function is advised in all diabetics. FORMINAL therapy should be stopped 2-3 days before surgery and before clinical investigations such as intravenous urography and intravenous angiography, and reinstated only after control of renal function has been regained. The use of FORMINAL is not advised in conditions, which may cause dehydration, or in patients suffering from serious infections, trauma or on low calorie intake. patients on long-term treatment with FORMINAL should have an annual estimation of vitamin B12 levels, since FORMINAL may cause vitamin b12 deficiencies which may result in megaloblastic anaemia. During concomitant treatment with a sulphonylurea, blood glucose should be monitored because combined therapy may cause hypoglycaemia. Stabilisation of diabetic patients with FORMINAL and insulin should

be carried out in hospital because of the possibility of hypoglycaemia until the ratio of the two drugs has been obtained. Contraindications should be carefully observed.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form"**, found online under SAHPRA's publications:
https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Hypoglycaemia can occur when FORMINAL is given concomitantly with a sulphonylurea, insulin or alcohol. In excessive dosage, and particularly if there is a possibility of accumulation, lactic acidosis may develop. Intense symptomatic and supportive therapy is recommended which should be particularly directed at correcting fluid loss and correcting blood glucose levels.

Treatment of overdosage:

There is no specific antidote for overdose with FORMINAL. Treatment is supportive and symptomatic and should be directed at correcting fluid loss and metabolic disturbances.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 21.2 Oral Hypoglycaemics

ATC code: A10BA02 Metformin

Metformin is a biguanide oral anti-hyperglycaemic agent. Its mode of action is thought to be

increased peripheral glucose utilisation mediated by increased insulin sensitivity and inhibition of increased hepatic and renal gluconeogenesis.

5.2 Pharmacokinetic properties

Absorption:

After an oral dose of metformin, T max is reached in 2.5 hours. Absolute bioavailability of a 500 mg or 850 mg metformin tablet is approximately 50 – 60 % in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20 – 30 %.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear.

At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 µg/ml. In controlled clinical trials, maximum metformin plasma levels (C max) did not exceed 4 µg/ml, even at maximum doses. Food decreases the extent and slightly delays the absorption of metformin; following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25 % decrease in AUC (area under the curve) and a 35-minute prolongation of time to peak plasma concentration were observed. The clinical relevance of these decreases is unknown.

Distribution:

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution ranged between 63 – 276 L.

Metabolism:

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination:

Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Maize starch

Povidone K-30

Purified water

Magnesium stearate

Film-coating:

Flexicoat SCH White Protect consisting of magnesium silicate hydroxide, titanium dioxide, polyvinyl alcohol-polyethylene glycol graft copolymer and polyvinyl alcohol (PVA), polyvinyl alcohol, silicon dioxide. Purifed water.

6.2 Incompatibilities

No incompatibilities.

6.3 Shelf life

HDPE containers and PVC/Al blister strips: 36 months.

LDPE Patient ready packs: 15 months.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light and moisture.

Keep HDPE container and patient ready pack tightly closed.

Do not remove tablets from container/blister strip until required for use.

Do not remove tablets from patient ready pack until required for use.

6.5 Nature and contents of container

FORMINAL 500 is supplied in

- White High Density Polyethylene (HDPE) bottles with an induction seal wad in the child resistant cap along with a silica gel desiccant in pack sizes of 60, 100 or 500 tablets.
- Clear, push-through PVC/Aluminium printed blister strips of 10 or 14 tablets each, packed into a unit-carton containing 56, 60, 84 or 100 tablets.
- Printed patient ready Low Density Polyethylene (LDPE) packs of 56 or 84 tablets.

FORMINAL 850 is supplied in

- White High Density Polyethylene (HDPE) bottles with an induction seal wad in the child resistant cap along with a silica gel desiccant in pack sizes of 60, 100 or 300 tablets.
- Clear, push-through PVC/Aluminium printed blister strips of 10 or 14 tablets each, packed into a unit-carton containing 56, 60, 84 or 100 tablets.
- Printed patient ready Low Density Polyethylene (LDPE) packs of 28, 56 or 84 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Gulf Drug Company (Pty) Ltd

22 Burnside Drive

Old Mill Industrial Park

Mount Edgecombe, 4300

8. REGISTRATION NUMBER

FORMINAL 500 - A38/21.2/0681

FORMINAL 850 - A38/21.2/0682

9. DATE OF FIRST AUTHORISATION

01 December 2006

10. DATE OF REVISION OF THE TEXT

14 March 2024

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